Express Mail Label No. EL405596413US 11-13-00 A

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
2290.00101
Total Pages in this Submission
98

JC966 U.S. PTO 11/10/00

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

GENE CLUSTER

JC813 U.S. PTO 09/710262 11/10/00

and invented by:

Eugene Rosenberg, Eliora Ron, Elisha Orr and Yossi Paitan

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☒ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: 09/240,537

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 32 pages and including the following:
   - a. ☒ Descriptive Title of the Invention
   - b. ☒ Cross References to Related Applications *(if applicable)*
   - c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   - d. ☐ Reference to Microfiche Appendix *(if applicable)*
   - e. ☒ Background of the Invention
   - f. ☒ Brief Summary of the Invention
   - g. ☒ Brief Description of the Drawings *(if drawings filed)*
   - h. ☒ Detailed Description
   - i. ☒ Claim(s) as Classified Below
   - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
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Total Pages in this Submission 98

Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*

   a. ☐ Formal b. ☒ Informal Number of Sheets 1

4. ☒ Oath or Declaration

   a. ☐ Newly executed *(original or copy)* ☐ Unexecuted

   b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

   c. ☒ With Power of Attorney ☐ Without Power of Attorney

   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☒ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche

7. ☒ Genetic Sequence Submission *(if applicable, all must be included)*

   a. ☒ Paper Copy

   b. ☐ Computer Readable Copy

   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers *(cover sheet & documents)*

9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☒ Information Disclosure Statement/PTO-1449 ☒ Copies of IDS Citations

12. ☒ Preliminary Amendment

13. ☒ Acknowledgment postcard

14. ☒ Certificate of Mailing

    ☐ First Class ☒ Express Mail *(Specify Label No.):* EL405596413US

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 2290.00101

Total Pages in this Submission 98

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1

17. ☐ Additional Enclosures *(please identify below)*:

Request That Application Not Be Published Pursuant To 35 U.S.C. 122(b)(2)

18. ☐ Pursuant to 35 U.S.C. 122(b)(2), Applicant hereby requests that this patent application not be published pursuant to 35 U.S.C. 122(b)(1). Applicant hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication of applications 18 months after filing of the application.

Warning

An applicant who makes a request not to publish, but who subsequently files in a foreign country or under a multilateral international agreement specified in 35 U.S.C. 122(b)(2)(B)(i), must notify the Director of such filing not later than 45 days after the date of the filing of such foreign or international application. A failure of the applicant to provide such notice within the prescribed period shall result in the application being regarded as abandoned, unless it is shown to the satisfaction of the Director that the delay in submitting the notice was unintentional.

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No. 2290.00101
Total Pages in this Submission

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	16	- 20 =	0	x $9.00	$0.00
Indep. Claims	8	- 3 =	5	x $40.00	$200.00
Multiple Dependent Claims (check if applicable) ☐					$0.00
				BASIC FEE	$355.00
OTHER FEE *(specify purpose)* _____					$0.00
				TOTAL FILING FEE	$555.00

☒ A check in the amount of **$555.00** to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **11-1449** as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated: **November 10, 2000**

Signature

Amy E. Rinaldo, Reg. No. 45,791
KOHN & ASSOCIATES
30500 Northwestern Highway, Suite 410
Farmington Hills, Michigan 48334
(248) 539-5050

cc:

Express Mail No. EL187077167US

Attorney's Docket Number: 2290.00074

Applicant or Patentee: Rosenberg et al.

Serial or Patent No:

Filed or Issued: Herewith

For: GENE CLUSTER

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(d)--SMALL BUSINESS CONCERN

I hereby declare that I am:

_____ the owner of the small business concern identified below:

__X__ an official of the small business concern empowered to act on behalf of the concern identified below:

Name of Concern: RAMOT-UNIVERSITY AUTHORITY FOR APPLIED RESEARCH AND INDUSTRIAL DEVELOPMENT, LTD.

Address of Concern: 32 Haim Levanon Street - P.O. Box 39296 Tel-Aviv 61392 Israel

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement: (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when, either directly or indirectly, one concern controls or has the power to control the other, or a third-party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention referenced above.

Described in:

_____ the specification filed herewith.

_____ application referenced above.

_____ patent referenced above.

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c), if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

* NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME: _____

ADDRESS: _____

_____

___ Individual ___ Small Business ___ Nonprofit Organization

NAME: _____

ADDRESS: _____

_____

___ Individual ___ Small Business ___ Nonprofit Organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28(b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

SIGNATURE: _____ **Date:** 2 June 1998

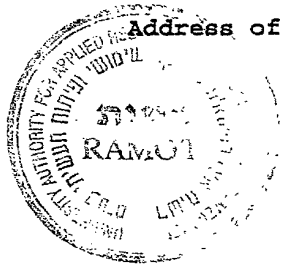
Hananel Kvatinsky
Manager-Patents Department

SIGNATURE: _____ **Date:** 2 June 1998

Rami Finkler
President/General Manager

Address of Persons Signing: 32 Haim Levanon Street

Tel Aviv 61392 ISRAEL



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Eugene Rosenberg, et al

Continuation of United States Patent
Application No. 09/240,537, filed: 01/29/99

Filed: Herewith

For: GENE CLUSTER

Attorney Docket No. 2290.00101

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231
Box Patent Application

Dear Sir:

Please preliminarily amend the above-captioned Continuation patent application prior to examination as follows:

IN THE SPECIFICATION:

Page 1, in the "Cross-Reference to Related Application Section", after "This is a", please insert:

--Continuation application of United States Patent Application Serial No.: 09/240,537, filed January 29, 1999, all of which is incorporated herein by reference--.

Page 3, line 17, please delete "1 and".

Page 4, line 12, after "DNA", please insert --and amino acid--.

IN THE CLAIMS:

1. (Twice Amended). A purified, isolated and cloned DNA or amino acid sequence encoding a polypeptide required for the synthesis of antibiotic TA [or a shorter polypeptide portion of said polypeptide] , said polypeptide being selected from the group consisting essentially of SEQ ID NOS 1-19 and analogs thereof.

3. (Twice Amended). A purified, isolated and cloned DNA or amino acid sequence consisting of a [DNA] sequence encoding a polypeptide required for post modification of antibiotic TA [or a shorter polypeptide portion of said polypeptide] said polypeptide being selected from the group consisting essentially of SEQ ID NOS 1-19 and analogs thereof.

5. (Amended) A purified, isolated and cloned DNA or amino acid sequence consisting of a [DNA] sequence encoding a gene product involved in a regulation of the biosynthesis of antibiotic TA said polypeptide being selected from the group consisting essentially of SEQ ID NOS 1-19 and analogs thereof.

7. (Twice Amended) A purified, isolated and cloned DNA sequence consisting of a DNA sequence as set forth in SEQ ID NO: [1 and] 2.

8. (Twice Amended) The DNA sequence of SEQ ID NO: [1 and] 2 altered by point mutations, deletions or insertions such that the resulting amino acid sequence is shortened.

Claim 9, line 1, please delete "1 or".

15. (Twice Amended) A method of combinatorial genetics using the TA genes as set forth in SEQ ID NOS 1-19 for use in combinatorial genetics.

16. (Twice Amended) A method of encoding for the synthesis, modification or regulation of antibiotic TA by using a TA gene as set forth in SEQ ID NOS 1-19 for encoding for the synthesis, modification or regulation of antibiotic TA.

REMARKS

Claims 1-16 are currently pending in the application. Claims 1, 3, 5, 7, 8, 9, 11 and 16 are in independent form.

The Office Action states that the Information Disclosure Statement filed on February 15, 2000 fails to comply with 37 CFR 1.198(a)(2), which requires a legible copy of each U.S. and foreign patent and each publication which is listed. Copies of the missing references are attached hereto.

Claims 1-6 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention.

The Office Action states that the instant claims are directed to DNA sequences encoding or partially encoding polypeptides for the synthesis, post-modification, and/or regulation of the antibiotic TA where the claimed products are defined by their functional characteristics. However, the Office Action holds that in claims to genetic material a generic statement such as "vertebrate insulin cDNA" without more is not an adequate written description of the genus since it does not distinguish the genus from others, except by function. The Office Action concludes that one skilled in the art cannot visualize or recognize the identity of the members of the genus. However, the claims as pending do state that there must be present a specific polypeptide which is utilized in the synthesis of antibiotic TA. This statement does sufficiently describe a structural feature commonly possessed by members of the genus such that the members of the genus must include therein at least one polypeptide which is utilized in the synthesis, post-modification or regulation of the antibiotic TA. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 7-9 and 10-14, stand rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action states that in the claims the sequence numbers are referred to as DNA sequences, while in the Sequence Listing they are referred to as amino acid sequences. This was an error found in the Sequence Listing, which error has been remedied with the attached Sequence Listing. This correction thus obviates the present rejection.

The Office Action states that claims 15 and 16 are rejected under 35 U.S.C. Section 101 because the claimed recitation of a use, without setting forth any further steps involved in the process, results in an improper definition of a process. Accordingly, both claims 15 and 16 have been amended to either recite a proper method claim or the language has been amended to no longer recite a method claim. Reconsideration of the rejection is respectfully requested.

Claims 1-2 stand rejected under 35 U.S.C. Section 102(b) as being anticipated by general scientific knowledge. The Office Action states that in claim 1, line 1, the claim to "DNA sequences partially encoding...polypeptides" without defining the term "partially" claims fragments as small as three nucleotides, or a single code, encoding one amino acid would be included in the claim. Furthermore, the Office Action states that the nucleotide database of GenBank

contains greater than 100 nucleotide sequences from the cited species at the time the invention was made, all of which anticipate claims 1-2. However, when read more specifically, none of the published sequences were required for the biosynthesis or post-modification of antibiotic TA. Additionally, there were no cited references teaching the claimed sequences. As a matter of law, there must be a reference cited which teaches subject matter even if the subject matter is held to be in the general knowledge. That is, any holding of a limitation being in the general knowledge must be supported by a citation. Since the prior art does not disclose any sequences for the biosynthesis or post-modification of antibiotic TA as recited in pending claims 1 and 2, the claims are not anticipated by the cited general scientific knowledge and reconsideration of the rejection is respectfully requested.

Claim 8 stands rejected under 35 U.S.C. Section 102(b), as being anticipated by general scientific knowledge. The Office Action cites that in claim 8, line 2, the claim recites DNA sequences resulting in truncated amino acid sequences. The Office Action states that without any further limitation of the term "truncated", this claim language broadly encompasses DNA fragments as small as three nucleotides, or a single code on which sequences are found throughout scientific literature. Claim 8 has been amended in order to further prosecution, to remove the term "truncated". Additionally, when read more specifically, none of the published sequences were required for the biosynthesis or post-modification

of antibiotic TA. As this requirement is recited in the claim language of pending claims 1 and 2, these claims are not anticipated by the cited general scientific knowledge. Reconsideration of the rejection is respectfully requested.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. The amendments overcoming the rejections under 35 USC 112 are made exactly as suggested by the Office Action. Claims have also been amended to clearly distinguish over the prior art. The application is made at least in better condition for appeal as the amendment removes many issues thereby simplifying the issues on appeal. That is, each and every rejection under 35 USC 112 has been overcome exactly as suggest in the Office Action. Further, the claims have been amended to more specifically define the invention while raising no new issues which would require any further searching. Rather, the amendments have been made in view of comments made in the Office Action which clearly distinguish the presently pending claims over the cited prior art. Hence, it is respectfully requested that the amendment be entered.

In conclusion, it is respectfully requested that the present amendment be entered in order to place the application in condition for allowance, which allowance is respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES

Amy E. Rinaldo
Registration No. 45,791
30500 Northwestern Hwy. Ste. 410
Farmington Hills, Michigan 48334
(248) 539-5050

Dated: November 10, 2000

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on November 10, 2000.

Connie Herty

GENE CLUSTER

BACKGROUND OF THE INVENTION

Polyketides constitute a large and highly diverse group of secondary metabolites synthesized by bacteria, fungi and plants, with a broad range of biological activities and medical applications. They include anti-cancer agents (Daunorubicin), antibiotics (tetracyclines, erythromycin etc.), immunosuppressants (macrolide FK506) and compounds with mycotoxic activity (aflatoxins, ochratoxins, ergochromes, patulin etc.). Polyketides are synthesized by repetitive condensations of acetate or propionate monomers in a similar way to that of fatty acid biosynthesis. Structural diversity of polyketides is achieved through different thioester primers, varying chain extension units used by the polyketide synthases (PKSs), and variations in the stereochemistry and the degree of reduction of intermediates. Diversity is also achieved by subsequent processing, such as alkylations, oxidations, O-methylations, glycosylations and cyclizations. Genetic studies indicated that gene organization of functional units and motif patterns of various PKSs are similar. This similarity was used to identify and obtain new PKS systems in both gram negative and gram positive bacteria.

PKS systems are classified into two types: type I PKSs are large, multifunctional enzymes, containing a separate site for each condensation or modification step. These represent "modular PKSs" in which the functional domains

encoded by the DNA sequence are usually ordered parallel to the sequence of reactions carried out on the growing polyketide chain. Type II PKSs are systems made up of individual enzymes, in which each catalytic site is used repeatedly during the biosynthetic process.

Genetic studies on prokaryotic PKSs have focused on gram positive microorganisms, particularly on actinomycetes. Myxobacteria are gram negative bacteria that produce a large number of secondary metabolites, including polyketides. *Myxococcus xanthus* produces TA (Rosenberg, et al., 1973; Rosenberg, et al., 1984), which is an antibacterial antibiotic.

The polyketide antibiotic Tel-Aviv (hereinafter TA) (Rosenberg, et al., 1973) is synthesized by the gram negative bacterium *Myxococcus xanthus* in a unique multi-step process incorporating a glycine molecule into the polyketide carbon chain, which is elongated through the condensation of 11 acetate molecules by a type I polyketide synthase (PKSs).

The antibiotic TA was crystallized and its chemical properties were determined. It is a macrocyclic polyketide synthesized through the incorporation of acetate, methionine, and glycine. It inhibits cell wall synthesis by interfering with the polymerization of the lipid-disaccharide-pentapeptide and its ability to adhere avidly to tissues and inorganic surfaces makes it potentially useful in a wide range of clinical applications, such as treating gingivitis.

A growing interest in the study of PKS systems and peptide synthetase systems stems from the need to develop new potent biologically active compounds. The use of combinatorial genetics in both systems (PKS and peptide synthetase) separately has led to the production of new polyketides and new peptides.

It would therefore by useful to be able to generate new biological agents from secondary metabolites of the antibiotic TA.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a purified, isolated and cloned DNA sequence partially encoding a functional portion of a polypeptide component required for the synthesis of antibiotic TA. Also provided are purified, isolated and cloned DNA sequences encoding a polypeptide component required for postmodification of antibiotic TA and encoding a gene product involved in the regulation of the biosynthesis of antibiotic TA. A purified, isolated and cloned DNA sequence having a DNA sequence (Seq. ID No:1 and 2) encoding a polypeptide component required for encoding the TA gene cluster and any mutations thereof is provided. Also provided are methods of using the TA genes for combinatorial genetics and of using the TA genes encoding for synthesis and modification or regulation of antibiotic TA.

DESCRIPTION OF THE DRAWING

Other advantages of the present invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein:

Figure 1 shows the physical maps of the DNA regions involved in TA synthesis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention consists of a DNA sequence of at least 42 kb encoding genes involved in TA production and *Myxococcus xanthus* as best shown in Seq. ID No:1 through 17 and cosmid clones containing the entire TA gene DNA sequences. The TA gene cluster has been purified, isolated, and cloned. The purification, isolation and cloning was done according to the methods described in Marshak et al, "Strategies for Protein Purification and Characterization. A laboratory course manual." CSHL Press, 1996.

A DNA fragment of at least 42 kb (Figure 1), encoding genes involved in TA production in *Myxococcus xanthus* has been identified, cloned and analyzed. These steps were done in accordance with Marshak et al, "Strategies for Protein Purification and Characterization. A laboratory course manual." CSHL Press, 1996. This

fragment contains a large region of about 20 kb, encoding the genes responsible for the regulation and the post-modification of TA. An additional fragment of approximately 8-10 kb located 10-20 kb downstream of the post-modification region, encodes the enzyme responsible for the incorporation of the glycine into the polyketide chain. This novel polypeptide is made up of a peptide synthetase unit lying between two PKS modules.

The potential of this unique polypeptide in combining the two systems can lead to a new family of compounds, emerging from various combinations which can be utilized for combinatorial genetics. Such utilization can produce, for example, new bioactive agents, new polyketides and new peptides. Additionally, the TA gene cluster can be utilized in a method for the synthesis, modification or regulation of the TA antibiotic.

Mutations imparting defects into the TA gene cluster can be point mutations, deletions or insertions. The mutations can occur within the nucleotide sequence of the allele of the TA gene cluster such that the resulting amino acid sequence of the TA gene cluster product is altered.

In one embodiment of the present invention, the TA gene cluster can be included in a vector or recombinant expression vector. This vector containing the TA gene cluster is able to transform a suitable eucaryotic or procaryotic host cell. A suitable host cell can be determined by one skilled in the art. An example of a

suitable cell which can be transformed by the TA gene cluster is an E. coli cell.

In another embodiment of the present invention, the a DNA fragment encoding the TA gene cluster can be cloned into a cosmid, as shown in Figure 1. This DNA fragment contains a large region of about 20kb, encoding the genes responsible for the regulation and the post-modification of TA. An additional fragment of approximately eight to ten kb is located 10-20 kb downstream of the post-modification region and encodes the enzyme responsible for the incorporation of the glycine into the polyketide chain. The novel polyketide chain is made up of a peptide synthetase unit lying between two PKS modules (See Figure 1).

The above discussion provides a factual basis for the use of the TA gene cluster. The methods used with and the utility of the present invention can be shown by the following non-limiting examples and accompanying figure.

EXAMPLES

GENERAL METHODS:

METHODS:

General methods in molecular biology: Standard molecular biology techniques known in the art and not specifically described are generally followed as in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Springs Harbor Laboratory, New York (1989, 1992), and in Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons, Baltimore, Maryland (1989). Polymerase

chain reaction (PCR) is carried out generally as in *PCR Protocols: A Guide To Methods And Applications*, Academic Press, San Diego, CA (1990). Reactions and manipulations involving other nucleic acid techniques, unless stated otherwise, are performed as generally described in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, and methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057 and incorporated herein by reference. In-situ (In-cell) PCR in combination with Flow Cytometry can be used for detection of cells containing specific DNA and mRNA sequences (Testoni et al, 1996, Blood 87:3822.)

Recombinant Protein Purification

Marshak et al, "Strategies for Protein Purification and Characterization. A laboratory course manual." CSHL Press, 1996.

Example 1:

Analysis of the TA gene cluster by chromosomal restriction map.

Chromosomal DNA of several transposition mutants (ER-2514, ER-1037, ER-1030, ER-1311, ER-7513, ER-3708, ER-4639 and ER-6199; Varon *et al.*, 1992) was extracted, digested with restriction enzymes that cut within the transposon, and analyzed by Southern hybridization with six different probes (originating from Tn*V* and Tn*5lac*). We used probes designed to hybridize either to the entire transposon, or to its 5' or 3' ends. A chromosomal restriction map of the whole gene cluster was constructed on the basis of these results (Figure 1). The data refined the transduction

map (Varon *et al.*, 1992) and further indicated that all the genes in the cluster are transcribed in the same direction (see Figure 1).

Preparation of TA-specific probes

DNA from the Tn*V* mutant ER-4639, ER1311 and ER-6199 was digested with *Kpn*I (does not restrict Tn*V*), self-ligated and transformed into *E. coli* XL1-Blue MR using the transposon-derived kanamycin resistance for selection. Tranformant clones pPYT4639, pPYT1311/p5 and pPYT6199 carried a 1.5 kb, 2.3 kb and a 11.2 kb fragment, respectively (see Figure 1).

Cloning of a *M. xanthus* DNA region encoding genes involved in TA biosynthesis.

A library of *M. xanthus* ER-15 was constructed in the cosmid vector SUPERCOS-1 and screened using specific TA probes obtained from transposition mutants (ER-4639, ER-1311 and ER-6199, see map) that contain a Tn*V* transposon. Seventy four recombinant cosmids that carried genes required for TA production were identified through colony hybridization. The cosmids, pPYCC64 and pPYCC44, which hybridized to these probes were further characterized through restriction analysis (see Figure 1) and sub cloned for sequencing.

Throughout this application, various publications, including United States patents, are referenced by author and year and patents by number. Full citations for the publications are listed below. The disclosures of these publications and patents in

their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

REFERENCES

1. Rosenberg, E., Vaks, B. and Zuckerberg. A. Bactericidal action of an antibiotic produced by Myxococcus xanthus. Antimicrob. Agents. Chemother. 4:507-513 (1973).

2. Rosenberg, E., Porter, J.M., Nathan, P.N., Manor, A. and Varon, M. Antibiotic TA: an adherent antibiotic. Bio/Technology. 2:796-799 (1984).

3. Varon *et al.*, 1992

4. Marshak et al, "Strategies for Protein Purification and Characterization. A laboratory course manual." CSHL Press, 1996.

5. Testoni et al, 1996, Blood 87:3822.

6. *PCR Protocols: A Guide To Methods And Applications*, Academic Press, San Diego, CA (1990).

7. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Springs Harbor Laboratory, New York (1989, 1992).

8. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley and Sons, Baltimore, Maryland (1989).

SEQ LISTING PAGE(s)

REGION 1:

Ta1 - Peptidesynthetase unit-PKS module.

FRAGMENT size(aa):2392

VDPARLTRAWEGLLERYPLLAGAIRVEGTEPVIVPSGQVSAEVHEVPSVSDSALVATLRASAKVPFDLAC
GPLARLHLYSRSEHEHVLLLCFHHLVLDGASVAPLLDALRERYAGTEAKAGLLEVPIVAPYRAAVEWEQ
LAIGGDEGRRHLDYWRHVLATPVPPPLNLPTDRPRSATGLDSEGATHSQRVPTEQALRLREFARAQQVS
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DNA sequence nucleotides 1-7178.

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ATGGCCATCGCGGGTGGAGTGAATCTCTACCTCCACCCGTCGAGCTACGTCAGCCTGTCCGGGCAGC
AGATGCTGTCGAC

REGION 2

TaR1 - Surface layer protein

From nucleotide 2955 to 601, size(aa): 785.

MKVVNKLLEKLPDVVAGKVPDVKLQDQDIKVPLAQGTFTEEKILPPKLAMHGFTLSFEATGEASIRNFNS
LGDVDENGIIGEPSPESAEPGPRPQLLLGSDIGWMRYQVSARVKAAVSASLSFLASENQTELSVTLSDYRA
HPLGQNMREAVRSDLSELRLMQATDLAKLTTGDAVAWHVRGALHTRLELNWADIFPTNLNRLGFLRGN
ELLALKTSAKAGLSARVSLTDDYQLSFSRPRAGRIQVAVRKVKSHEQALSAGLGITVELLDPATVKAQLG
QLLEALLGPVLRDLVKKGTTAVEIMDGLVDKASKAKLDDNQKKVLGLVLERLGIDPQLADPANLPQAW
ADFKARVAESLENAVRTQVAEGFEYEYLRLSETSTLLEVVVEDVTAMRFHESLLKGNLVELLKWMKSLP
AQQSEFELRNYLHATTLTRQQAIGFSLGLGSFELLKAKNVSKQSWVTQENFQGARRMAFLGRRGYEDKL
LGTRGQWVVDLKADMTRFSPTPVASDFGYGLHLMLWGRQKKLSRKDLQQAVDDAVVWGVLDAKDA
ATVISTMQEDMGKHPIETRLELKMADDSFRALVPRIQTLELSRFSRALARALPWSEQLPRASAEFRRAVY
APIWEAYLREVQEQGSLMLNDLSPSRAAQIAKWYFQKDPTVRDLGKDLQLIESEWRPGGGNFSFAEVIS
KNPNTLMRCRNFVSGMVRLRRAIDERKAPDELRTVFGELEGMWTTGFHLRAAGSLLSDLAQSTPLGLAG
VERILTVRVADSEEQLVFSTARSTGAA

TaR2 - two component system, response regulator

From nucleotide 3116 to 4702, size(aa): 529.

MPSGCYGAASAFVLPPLPAMPQAPSDVSQVLLPFGGLVGREVDLDAFLQTLMDRIAITLQADRGTLWLL
DPARRELFSRAAHLPEVSQIRVKLGQGVAGTVAKAGHAINVPDPRGEQRFFADIDRMTGYRTTSLLAVPL
RDGDGALYGVLQVLNRRGEDRFTDEDTQRLTAIASQVSTALQSTSLYQELQRAKEQPQVPVGYFFNRIIG
ESPQLQAIYRLVRKAAPTDATVLLRGESGSGKELFARAVHVNGPRRDQPFIKVDCAALPATLIENELFGH
ERGAFTGADHRVPGKFEAASGGTVFIDEIGELPLPVQGKLLRVIQDREFERVGGTQAVKVDVRIVAATHR
DLARMVAEGRFREDLYYRIKVVEVVLPPLRERGAEDIERLARHFVAAVARRHRLTPPRLSAAAVERLKR
YRWPGNVRELENCIESAVVLCEGEILEEHLPLPDVDRAALPPPAAAQGVNAPTAPAPLDAGLLPLAEVER
RHILRVLDAVKGNRTAAARVLAIGRNTLARKLKEYGLGDEP

TaR3 - two component system, kinase sensor.

From nucleotide 5595 to 4720, size(aa): 292

MRASQAEAPHSRRLTMEVRFHGVRGSIAVSGSRIGGNTACVEVTSQGHRLILDAGTGIRALGEIMMREG
APQEATLFFSHLHWDHVQGFPFFTPAWLPTSELTLYGPGANGAQALQSELAAQMQPLHFPVPLSTMRSR
MDFRSALHARPVEVGPFRVTPIDVPHPQGCLAYRLEADGHSFVYATDVEVRVQELAPEVGRLFEGADVL
CLDAQYTPDEYEGRKGVAKKGWGHSTMMDAAGVAGLVGARRLCLFHHDPAHGDDMLEDMAEQARA
LFPVCEPAREGQRLVLGRAA

TaA - NUS-G like transcription antitermination.

From nucleotide 6290 to 6793, size(aa): 168

MPGPRCAENDWVALLVRVNHEKVAAAQLGKHGYEFFLPTYTPPKSSGVKAKLPLFPGYLFCRYQPLNP
YRIVRAPGVIRLLGGDAGPEAVPAQELEAIRRVADSGVSSNPCDYLRVGQRVRIIEGPLTGLEGSLVTSKS
QLRFIVSVGLLQRSVSVEVSAEQLEPITD

TaB - acyl carrier protein (ACP).

From nucleotide 6870 to 7106, size(aa): 79

MDKRIIFDIVTSSVREVVPELESHPFEPEDDLVGLGANSLDRAEIVNLTLEKLALNIPRVELIDAKTIGGLV
DVLHARL

TaC - beta-ketoacyl [ACP] synthase III (KAS III, FabH)

From nucleotide 7119 to 8378, size(aa): 420

MGPVGIEAMNAYCGIARLDVLQLATHRGLDTSRFANLLMEEKTVPLPYEDPVTYGVNAARPILDQLTAA
ERDSIELLVACTESSFDFGKAMSTYLHQHLGLSRNCRLIELKSACYSGVAGLQMAVNFILSGVSPGAKAL
VVASDLSRFSIAEGGDASTEDWSFAEPSSGAGAVAMLVSDTPRVFRVDVGANGYYGYEVMDTCRPVAD
SEAGDADLSLLSYLDCCENAFREYTRRVPAANYAESFGYLAFHTPFGGMVKGAHRTMMRKFSGKNRGD
IEADFQRRVAPGLTYCQRVGNIMGATMALSLLGTIDHGDFATAKRIGCFSYGSGCSSEFFSGVVTEEGQQ
RQRALGLGEALGRRQQLSMPDYDALLKGNGLVRFGTRNAELDFGVVGSIRPGGWGRPLLFLSAIRDFHR
DYQWIS

TaD - membrane associated protein

From nucleotide 8404 to 9378, size(aa): 325

MSSVATAVPLTARDSAVSRRLRITPSMCGQTSLFAGQIGDWAWDTVSRLCGTDVLTATNASGAPTYLAF
YYFRIRGTPALHPGALRFGDTLDVTSKAYNFGSESVLTVHRICKTAEGGAPEADAFGHEELYEQPQPGRI
YAETFNRWITRSDGKSNESLIKSSPVGFQYAHLPLLPDEYSPRRAYGDARARGTFHDVDSAEYRLTVDRF
PLRYAVDVIRDVNGVGLIYFASYFSMVDWAIWQLARHQGRSEQAFLSRVVLDQQLCFLGNAALDTTFDI
DVQHWERVGGGEELFNVKMREGAQGRDIAVATVKVRFDAASEGGRRG

TaE - acyl carrier protein (ACP).

From nucleotide 9386 to 9364, size(aa): 82

MTDEQIRGVVHQSIVRVLPRVRSNEIAGHLNLRELGADSVDRVEILTSILDSLRLQKTPLAKFADIRNIDAL
VAFLAGEVAGG

TaF - beta-ketoacyl [ACP] synthase III (KAS III, FabH)

From nucleotide 9757 to 10878, size(aa): 374

MMQERGVALPFEDPVTNAVNAARPILDAMSPEARERIELLVTSSESGVDFSKSISSYAHEHLGLSRHCRFL
EVKQACYAATGALQLALGYIASGVSPGAKALVIATDVTLVDESGLYSEPAMGTGGVAVLLGDEPRVMK
MDLGAFGNYSYDVFDTARPSPEIDIGDVDRSLFTYLDCLKHSFAAYGRRVDGVDFVSTFDYLAMHTPFA
GLVKAGHRKMMRELTPCDVDEIEADFGRRVKPSLQYPSLVGNLCSGSVYLSLCSIIDTIKPERSARVGMF
SYGSGCSSEFFSGVIGPESVSALAGLDIGGHLRGRRQLTFDQYVELLKENLRCLVPTKNRDVDVERYLPL
VTRTASRPRMLALRRVVDYHRQYEWV

TaG - signal peptidase II (LSPA)

From nucleotide 10909 to 11421, size(aa): 171

MNTPSLTNWPARLGYLLAVGGAWTAADQVTKQMARDGAKRPVAVFDSWWHFHYVENRAGAFGLFSS
FGEEWRMPFFYVVGAICIVLLIGYYFYTPPTMKLQRWSLATMIGGALGNYVDRVRLRYVVDFVSWHVG
DRFYWPSFNIADTAVVVGAALMILESFREPRQQLSPG

TaH - cytochrome P450 hydroxylase (cP450)

From nucleotide 11473 to 12897, size(aa): 475

MGTSEPVEPDHALSKPPPVAPVGAQALPRGPAMPGIAQLMMLFLRPTEFLDRCAARYGDTFTLKIPGTPP
FIQTSDPALIEVIFKGDPDLFLGGKANNGLKPVVGENSLLVLDGKRHRRDRKLIMPTFLGERMHAYGSVI
RDIVNAALDRWPVGKPFAVHEETQQIMLEVILRVIFGLEDARTIAQFRHHVHQVLKLALFLFPNGEGKPA
AEGFARAVGKAFPSLDVFASLKAIDDIIYQEIQDRRSQDISGRQDVLSLMMQSHYDDGSVMTPQELRDEL
MTLLMAGHETSATIAAWCVYHLCRHPDAMGKLREEIAAHTVDGVLPLAKINELKFLDAVVKETMRITP
VFSLVARVLKEPQIIGGTTYPANVVLSPNIYGTHHRADLWGDPKVFRPERFLEERVNPFHYFPFGGGIRK
CIGTSFAYYEMKIFVSETVRRMRFDTRPGYHAKVVRRSNTLAPSQGVPIIVESRLPS

TaI - malonyl CoA [ACP] transacylase (MCT, FabD)

From nucleotide 12938 to 13891, size(aa): 318

MVDSVSKQARRKVFLFSGQGTQSYFMAKELFDTQTGFKRQLLELDEQFKQRLGHSILERIYDARAARLD
PLDDVLVSFPAIFMIEHALARLLIDRGIQPDAVVGASMGEVAAAAIAGAISVDAAVALVAAQAQLFARTA
PRGGMLAVLHELEACRGFTSVARDGEVAAINYPSNFVLAADEAGLGRIQQELSQRSVAFHRLPVRYPFHS
SHLDPLREEYRSRVRADSLTWPRIPMYSCTTANRVHDLRSDHFWNVVRAPIQLYDTVLQLEGQGGCDFI
DVGPAASFATIIKRILARDSTSRLFPLLSPSPASTGSSMG

TaJ - malonyl CoA [ACP] transacylase (MCT, FabD)

From nucleotide 13909 to 14898, size(aa): 330

MTEAPAPRAPAQVPPPPSSPWALHTRGAASAPVNARKAALFPGQGSQERGMGAALFDEFPDLTDIADAI
LGYSIKRLCLEDPGKELAQTQFTQPALYVVNALSYLKRLREGAEQPAFVAGHSLGEYNALLVAGAFDFE
TGLRLVKRRGELMSGASGGTMAAVVGCDAVAVEQVLRDRQLTSLDIANINSPDQIVVSGPAQDIERARQ
CFVDRGARYVPLNVRAPFHSRYMQPAASEFERFLSQFQYAPLRCVVISNVTGRPYAHDNVVQGLALQLR
SPVQWTATVRYLLEQGVEDFEELGPGRVLTRLITANKRGAPAPATAAPAKWANA

TaK - 3-oxoacyl [ACP] synthase (KAS I, FabB)

From nucleotide 14963 to 16213, size(aa): 417

MSTSPVQELVVSGFGVTSAIGQGAASFTSALLEGAARFRVMERPGRQHQANGQTTAHLGAEIASLAVPE
GVTPQLWRSATFSGQAALVTVHEAWNAARLQAVPGHRIGLVVGGTNVQQRDLVLMQDAYRERVPFLR
AAYGSTFMDTDLVGLCTQQFAIHGMSFTVGGASASGLLAVIQAAEAVLSRKVDVCIAVGALMDVSYWE
CQGLRAMGAMGTDRFAREPERACRPFDRESDGFIFGEACGAVVVESAEHARRRGVTPRGILSGWAMQL
DASRGPLSSIERESQVIGAAIRHADLAPERVDYVNPHGSGSRQGDAIELGALKACGLTHARVNTTKSITG
HGLSSAGAVGLIATLVQLEQGRLHPSLNLVDPIDSSFRWVGATAEAQSLQNALVLAYGFGGINTAVAVR
RSATES

TaL - enoyl CoA hydratase.

From nucleotide 16224 to 17009, size(aa): 262

MQAASPPHRDYQTLRVRFEAQTCFLQLHRPDADNTISRTLIDECQQVLTLCEEHATTVVLEGLPHVFCM
GADFRAIHDRVDDGRREQGNAEQLYRLWLQLATGPYVTVAHVQGKANAGGLGFVSACDIVLAKAEVQ
FSLSELLFGLFPACVMPFLARRIGIQRAHYLTLMTRPIDAAQALSWGLADAVDADSEKLLRLHLRRLRCLS
KPAVTQYKKYASELGGQLLAAMPRAISANEAMFSDRATLEAIHRYVETGRLPWES

TaM - enoyl CoA hydratase.

From nucleotide 17000 to 17767, size(aa): 256

MGIMTEGTPMAPVVTLHEVEEGVAQITLVDRENKNMFSEQLVRELITVFGKVNGNERYRAVVLTGYDT
YFALGGTKAGLLSICDGIGSFNVTNFYSLALECDIPVISAMQGHGVGGGFAMGLFADFVVLSRESVYTTN
FMRYGFTPGMGATYIVPKRLGYSLGHELLLNARNYRGADLEKRGVPFPVLPRKEVLPHAYEIARDLAAK
PRLSLVTLKRHLVRDIRRELPDVIERELEMHGITFHHDDVRRRIEQLFL

TaN - O-methyltransferase (fragment).

From nucleotide 17782 to 19053, size(aa): 423

MLNLINNHAHGYVVTPVVLACNDAGLFELLRQGPKDFDRLAEALRANRGHLRVAMRMFESLGWVRRD
ADDVYAVTAAAAAAHRSFPREAQSLFALPMDRYLRGEDGLSLAPWFERSRASWDTDDTLVRELLDGAIIT
PLMLALEQRGGLKEARRLSDLWSGGDGRDTCVPEAVQHELAGFFSAQKWTREDAVDAELTPKGAFIFE
RALLFAIVGSYRPMLASMPQLLFGDCDQVFGRDEAGHELHLDRTLNVIGSGHQHRKYFAELEKLIITVFD
AENLSAQPRYIADMGCGDGTLLKRVYETVLRHTRRGRALDRFPLTLIAADFNEKALEAAGRTLAGLEHV
ALRADVARPDRLIEDLRARGLAEPENTLHIRSFLDHDRPYQPPADRAGLHARIPFDSVFVGKAGQEVVPA
EVFHSLVEHLE

DNA sequence 1-19053

GTCGACGTTGACGTCGCCCGGTGGCGTGCCGTGTGTCTTCTTCGACGCGGAGGTGCGCGAGGTGGCG
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CLAIMS

What is claimed is:

1. A purified, isolated and cloned DNA sequence partially encoding a functional portion of a polypeptide component required for the synthesis of antibiotic TA.

2. The DNA sequence according to claim 1, wherein said sequence is isolated from *Myxococcus xanthus*.

3. A purified, isolated and cloned DNA sequence consisting of a DNA sequence encoding a polypeptide component required for postmodification of antibiotic TA.

4. The DNA sequence according to claim 3, wherein said sequence is isolated from *Myxococcus xanthus*.

5. A purified, isolated and cloned DNA sequence consisting of a DNA sequence encoding a gene product involved in the regulation of the biosynthesis of antibiotic TA.

6. The DNA sequence according to claim 5, wherein said sequence is isolated from *Myxococcus xanthus*.

7. A purified, isolated and cloned DNA sequence consisting of a DNA sequence (Seq. ID No:1 and 2) encoding a polypeptide component required for encoding the TA gene cluster.

8. The DNA sequence of Seq. ID No:1 and 2 altered by point mutations, deletions or insertions such as the resulting amino acid sequence is truncated.

9. A transformed *E coli* carrying Seq. ID No:1 and 2.

10. A vector which comprises the DNA according to claim 7.

11. A host cell, wherein the host cell is selected from the group of suitable eucaryotic and procaryotic cells, which is transformed with the vector according to claim 10.

12. The host cell according to claim 11 which is *E. coli*.

13. A recombinant expression vector comprising a DNA sequence according to claim 7.

14. A cosmid containing the DNA sequence according to claim 7.

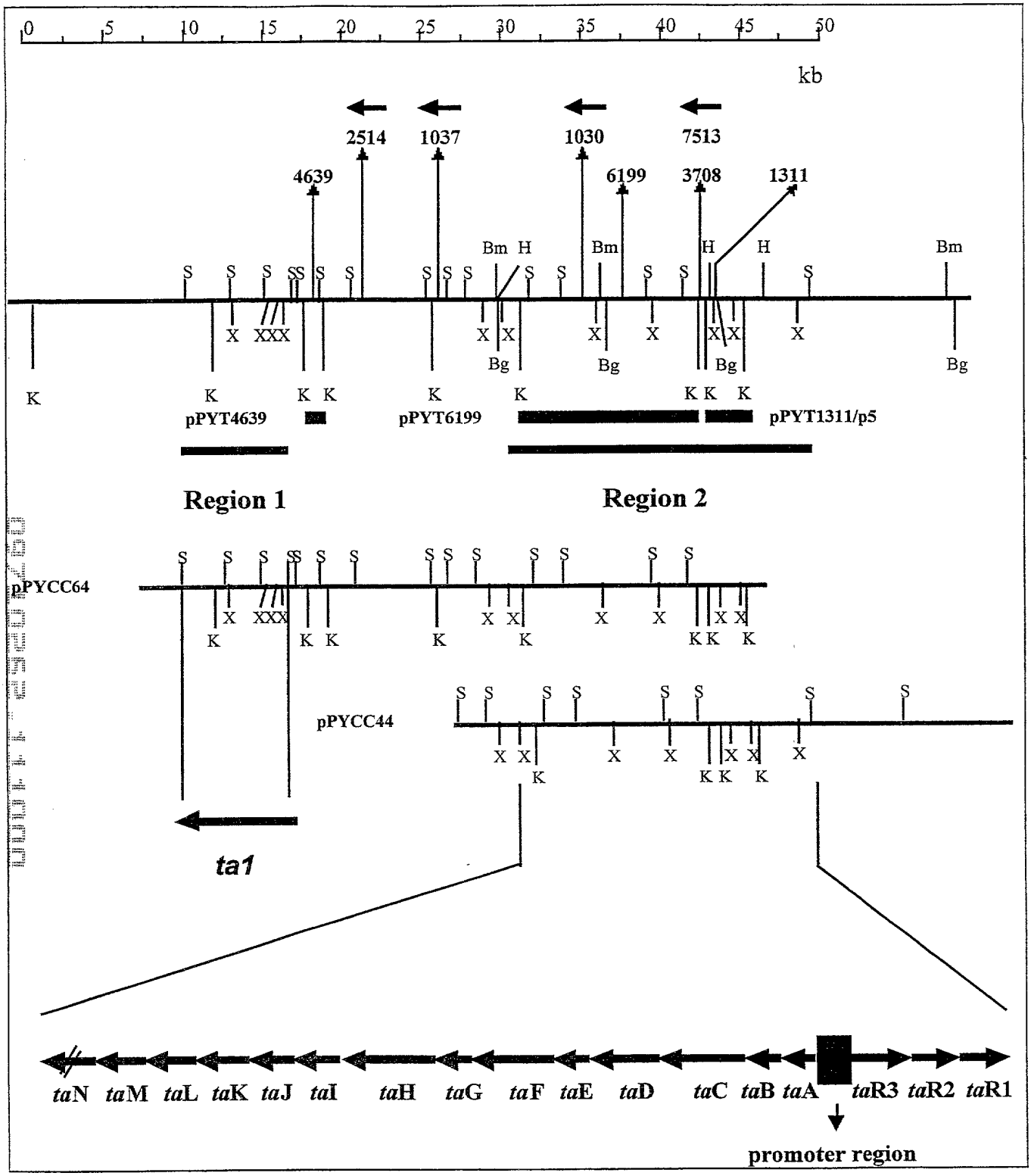
15. A method of using the TA genes for combinatorial genetics.

16. A method of using the TA genes encoding for the synthesis, modification or regulation of antibiotic TA.

TITLE

ABSTRACT OF THE DISCLOSURE

There is provided a purified, isolated and cloned DNA sequence partially encoding a functional portion of a polypeptide component required for the synthesis of antibiotic TA. Also provided are purified, isolated and cloned DNA sequences encoding a polypeptide component required for postmodification of antibiotic TA and encoding a gene product involved in the regulation of the biosynthesis of antibiotic TA. A purified, isolated and cloned DNA sequence having a DNA sequence (Seq. ID No:1 and 2) encoding a polypeptide component required for encoding the TA gene cluster and any mutations thereof is provided. Also provided are methods of using the TA genes for combinatorial genetics and of using the TA genes encoding for synthesis and modification or regulation of antibiotic TA.


0 5 10 15 20 25 30 35 40 45 50
kb
2514
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7513
4639
6199
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1311
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pPYT1311/p5
Region 1
Region 2
pPYCC64
pPYCC44
ta1
taN taM taL taK taJ taI taH taG taF taE taD taC taB taA taR3 taR2 taR1
promoter region

Docket No.
2290.00076

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

GENE CLUSTER

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **January 29, 1999** as United States Application No. or PCT International Application Number 09/240,537

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Fifth inventor's signature Date
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Sixth inventor's signature Date
Residence
Citizenship
Post Office Address